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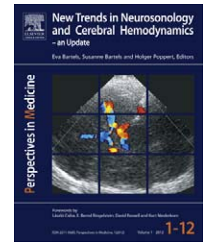

Italian multicenter study on venous hemodynamics in multiple sclerosis: Advanced Sonological Protocol

Giovanni Malferrari[a], **Massimo Del Sette**[b], **Marialuisa Zedde**[a,*], **Sandro Sanguigni**[c], **Nicola Carraro**[d], **Claudio Baracchini**[e], **Marcello Mancini**[f], **Erwin Stolz**[g,h]

[a] *Neurology Unit, Department of Neuromotor Physiology, Azienda Ospedaliera ASMN, Istituto di Ricovero e Cura a Carattere Scientifico, Viale Risorgimento 80, 42100 Reggio Emilia, Italy*
[b] *Neurology Unit, Ospedale Sant'Andrea, Via Vittorio Veneto 197, 19100 La Spezia, Italy*
[c] *Neurology Unit, Ospedale Madonna del Soccorso, Via Silvio Pellico 68, 63039 San Benedetto del Tronto, Italy*
[d] *Neurology Unit, Ospedala Cattinara, via Farneto 3, 34142 Trieste, Italy*
[e] *Neurology Unit, Azienda Ospedaliera di Padova, Via Nicolò Giustiniani 2, 35121 Padova, Italy*
[f] *Consiglio Nazionale delle Ricerche, Istituto di Biostrutturee Bioimmagini, University Federico II, via Pansini 5, 80131 Napoli, Italy*
[g] *Justus-Liebig University, Giessen, Germany*
[h] *Caritasklinik St. Theresia, Neurologische Klinik, Universisty of Saarlands, Germany*

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Transient global amnesia

Summary Because of the recent hypothesis of involvement of the venous hemodynamics in multiple sclerosis (MS), and because of the pitfalls of these studies, there is the need to achieve a definite conclusion from a large sample of subjects by using a strict and controlled neurosonological protocol. The aim of the advanced protocol, designed for a subgroup of the FISM study, is to analyze several items of the venous hemodynamics in order to obtain more pathophysiological data on venous circulation. *Advanced Ultrasound Protocol*: This is a multicenter, observational study. From a pool of about 1200 adults with MS, 400 healthy subjects and 400 subjects with other neurodegenerative disorders (2000 subjects in total) will be selected a population able to be examined by the advanced protocol. The examiner will always be blind on the clinical diagnosis, and the exams will be performed according to a standard protocol, whose measurements are mandatory for all participating centers. The advanced protocol is on a voluntary basis and it is optional. It includes, besides the basic one, measurements of blood flow volumes in carotid and vertebral arteries and in jugular and vertebral veins (inflow and outflow), with the definition of the drainage pattern. The ultrasound examination at each clinical site will

Abbreviations: BF, blood flow; BVR, basal vein of rosenthal; CCSVI, chronic cerebro spinal venous insufficiency; CSA, cross-sectional area; △CSA, difference between J2 IJV CSA in upright position and J2 IJV CSA in supine position; FISM, Italian Foundation on Multiple Sclerosis; ICA, internal carotid artery; IJV, internal jugular vein; MRI, magnetic resonance imaging; MS, multiple sclerosis; SRS, straight sinus; TAV, time averaged velocity; TCCS, transcranial color-coded duplex sonography; TS, transverse sinus; VA, vertebral artery; VV, vertebral vein.

* Corresponding author. Tel.: +39 0522 296494.
E-mail addresses: zedde.marialuisa@asmn.re.it, marialuisa.zedde@tiscali.it (M. Zedde).

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be followed by a second centralized blinded evaluation. The prevalence of CCSVI in MS will be estimated, with confidence intervals at 95%, and compared with the prevalence in other groups. Moreover, multiple analysis will be done comparing venous hemodynamics in the three different groups.

Introduction

Recently a vascular hypothesis about the cause of MS was proposed [1,2], pursuing the impairment of the cerebral venous drainage as a main factor in determining the manifestation of the disease and the disability, through the combination of multiple site venous lesions, mainly in the extracranial location. Five criteria were elaborated for the ultrasound identification of the more significant venous abnormalities (four criteria for the extracranial veins and one criterion for the intracranial veins), and the authors proposed that the presence of two or more positive criteria are diagnostic for a congenital malformation of the venous outflow, called by them CCSVI [2,3]:

1. reflux constantly present in IJV or vertebral veins (VVs) with the head at 0° and 90° assessed as flow reversal from its physiologic direction for a duration of >0.88 s during a short period of apnea following a normal exhalation
2. reflux in deep cerebral veins assessed as the presence of flow reversal for a duration of >0.50 s during normal breathing
3. high-resolution B-mode ultrasound evidence of proximal stenosis of the internal jugular vein (CSA < 0.3 cm^2)
4. flow not Doppler detectable in the IJVs or VVs despite numerous deep inspirations with the head positioned at 0° and 90°
5. reverted postural control of the main cerebral venous outflow (negative ΔCSA)

Both the careful reading and analysis of the ultrasound protocol described and applied by the proposing authors [1,2] and the negative findings of standardized ultrasound studies from other groups [4—7], raised many doubts about the ability of these criteria to provide a reliable evaluation of the cerebral venous hemodynamics. These considerations suggested to make efforts for identifying, applying and validating other ultrasound-assessable items for describing the venous hemodynamics.

FISM, a non-profit organization, is the promoter of a multicentre study, with the aim of obtaining the best response about the proposed hypothesis of a venous involvement in for people with MS worldwide. It will be possible through a study of large sample size to estimate the prevalence of venous abnormalities in MS, compared with the observed rate in normal controls and in patients affected by other neurologic diseases.

In this context, the distinctive features of the present study and previous studies comparing the current state of knowledge are as follows:

1. multicenter observational study with blinded ultrasound examination;
2. sample size of at least 1200 MS people
3. assessment of the prevalence of CCSVI and other forms of changes of venous hemodynamics in clinically isolated syndrome, relapsing-remitting, primary progressive and secondary progressive MS, using a larger sample than the one used to date.

A standardized ultrasound examination protocol was designed and implemented in a detailed training phase of the sinologist of the participating centres. The ultrasound protocol was distinguished in a basic protocol and an advanced protocol. The proposal of an advanced protocol came from the consideration that the assessment of the cerebral venous hemodynamics, both in intracranial and in extracranial pathways, does not mean only CCSVI, but it involves a global balance of the cerebral venous system (blood outflow patterns), validated measurement of valve function and a complete evaluation of the intracranial pathways and other items.

The topic of this paper is to provide some details about the advanced items of the ultrasound evaluation of the cerebral venous hemodynamics, starting from the critical evaluation of the five criteria proposed by Zamboni et al. for the diagnosis of CCSVI [1,2], with the aim of overcoming their limitations and finding the more proper items to evaluate the physiology and pathology of the cerebral venous hemodynamics.

Advanced ultrasound protocol

The definition of a more detailed and advanced study of the venous hemodynamics started from the highlight of the limitations and pitfalls of the proposed CCSVI criteria [1,2] and continued with the proposal of an alternative method to overcome them, considering the ultrasound methodological items from the literature.

Criterion 1

One of the main pitfalls of the criterion 1 is that the proposed temporal threshold for the jugular and vertebral reflux is validated only in other conditions, i.e. at the site of the valve leaflets of the IJV and with the Valsalva maneuver (Fig. 1), and not in other breath conditions and outside the valve level for the IJV and other veins [8,9].

Another doubtful aspect in the published studies with their description of the ultrasound protocol is the measurement of the reflux duration, because of the lack of mentioning and image documentation of the corresponding Doppler waveform.

Although breathing is a known factor affecting the venous hemodynamics, both in the neck and in the brain, there is not a validated ''breathing activation maneuver'', measurable, repeatable and reliable. Instead the Valsalva maneuver

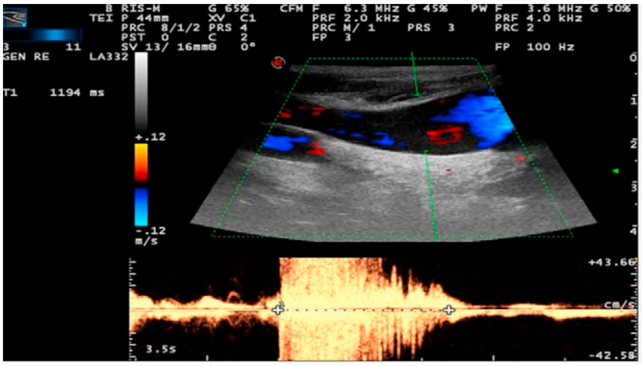

Figure 1 IJV valve incontinence lasting >0.88 s, elicited by a Valsalva maneuver.

is validated, executable in a measurable manner, with verifiable effects on IJV size and flow. Finally the threshold of 0.88 s is validated for diagnosing a significant valve incompetence of the IJV and it is not validated in other contexts and with other maneuvers.

Therefore, if the basic protocol contemplates the Valsalva maneuver as mandatory at the valve level, the advanced protocol added it along the extracranial course of IJV, at the level of its middle (J2) and distal (J3) segments. Outside the valve level there is not a validated threshold for a significant incontinence and maybe The inversion of the physiological flow direction during a Valsalva maneuver could not be called ''reflux'', but ''truncular incontinence''.

The execution of the Valsalva maneuver and its effects on volume and blood flow are well codified, also in mathematical models, both in supine and standing position, and both in the jugular and vertebral axis [10].

Fig. S1 shows the consequences of Valsalva maneuver also at middle (J2) and distal (J3) IJV segments of the IJV. But, why perform the Valsalva maneuver also in J2—J3 segments? The existence of a «truncular» jugular insufficiency is documented in patients with transient global amnesia with ultrasound techniques and the retrograde extent of this venous reflux into the sygmoid sinus has been found in this subgroup of patients by MRI [11—13].

Criterion 2

The main pitfall of this criterion is that Zamboni et al. [1,2] derived the threshold of >0.5 s from phlebological studies in CVI where it serves to quantify venous valve insufficiency following deflation of a tourniquet. Moreover the identification of the so-called intracranial reflux was performed by using a not validated window. In this study the known and validated temporal bone window will be used and in the advanced protocol also the TS is insonated, ipsi- or controlaterally.

The BVR is a virtually constant vein and it is very difficult to have abnormal flow patterns in it as a localized disease, outside cerebral vein thrombosis, particularly thrombosis of the SRS. The TS is characterized by a higher variability and it can be considered as a direct continuation to the IJV axis. Fig. S2 shows an abnormal flow direction in the Doppler waveform of the transverse sinus, as incidental finding in an asymptomatic subject.

Criterion 3

The main pitfalls of this criterion is that it was not defined consistently by Zamboni et al., because there are at least two different definition used in different papers:

- ΔCSA of <0.3 cm^2 [1]
- A local CSA reduction of >50% [2]

The first published studies of Zamboni et al. cited the paper of Lichtenstein et al. [14] as reference for the ultrasound diagnostic threshold of IJV stenosis, but the aim of the study was to assess the asymmetry of size of IJVs for selecting the best side to central venous catheterization, in 80 patients from Intensive Care Unit. Furthermore the asymmetry does not mean stenosis and the selected CSA for making the catheterization difficult is 0.4 cm^2. Moreover in angiographic studies of Zamboni et al. [15] there is not a pressure gradient across the venous stenosis.

In this protocol the threshold of CSA < 0.3 cm^2 was selected, coupled by a documentation of velocity parameters from a Doppler waveform.

In Fig. 2 there is an example of a positive criterion 3, but with a doubtful differential diagnosis between a so-called ''stenosis'' and a more physiological IJV hypoplasia.

Fig. 3 shows an ultrasound example of a real stenosis of the IJV at the valve level, in comparison with the MR venography of the same asymptomatic patient.

Criterion 4

The main pitfalls of this criterion derive from a general and nonspecific definition of this criterion. The authors [1,2] derived its validation from a study about extrajugular venous drainage pathways [16], comparing ultrasound and MRI and defining three types of venous drainage patterns: a total jugular volume flow of more than 2/3 (type 1), between 1/3 and 2/3 (type 2) and less than 1/3 (type 3) of the global arterial blood flow.

Moreover, in this study flow assessments were performed at rest and not during deep inspiration [17]. The documentation of a condition near to the ''blocked'' flow of the criterion 4 is provided in another pathological conditions, transient global amnesia, as a segmental IJV absence of flow with a reversed flow direction in IJV branches [12,13].

In Fig. 4, an example of this condition is shown in a patient with transient global amnesia. It is notable that the majority of so-called blocks are strictly positional conditions, often reversed by the ipsi- or contralateral tilting of the neck. For this reason in the present protocol, special attention was paid for avoiding to define a ''blocked'' flow in IJV if this condition was reversed by a minimal neck rotation.

It is also interesting to note that the situation described in Fig. 2 may gain two points, if the absence of flow is present in supine and upright positions, 1 for the criterion 3 and 1 for the criterion 4.

A global hemodynamics of the venous system rather than single segment evaluation is the aim; therefore a useful and validated tool is the calculation of the arterial blood flow and venous blood flow, as used in literature for distinguishing

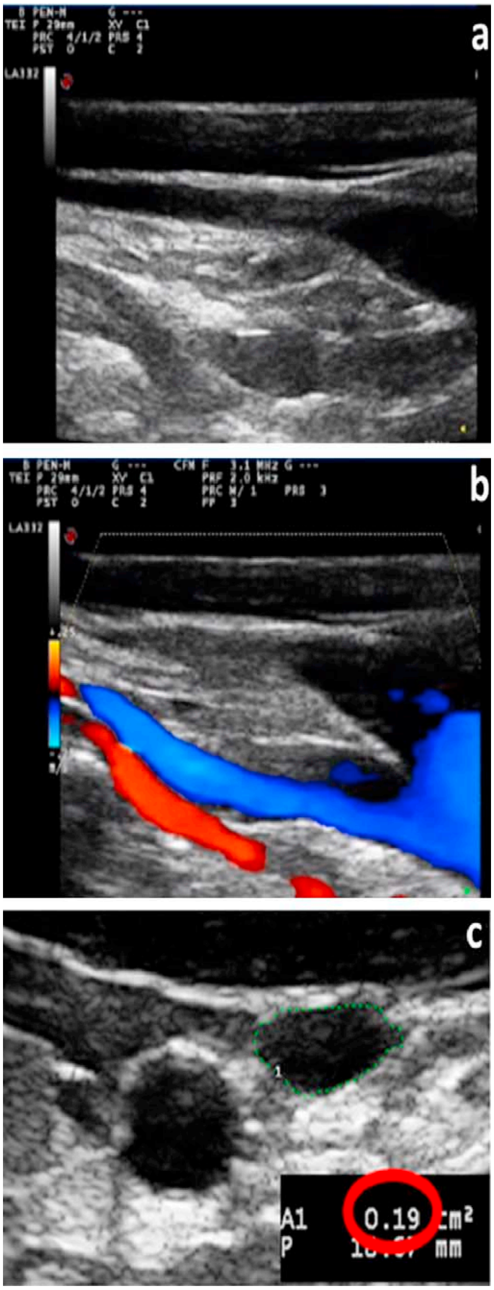

Figure 2 Example of the positivity of criterion 3. (a) B-mode ultrasound examination of the IJV in longitudinal scan. (b) Color-mode ultrasound examination of the IJV in longitudinal scan. (c) CSA measurement at J2 IJV level in transverse scan.

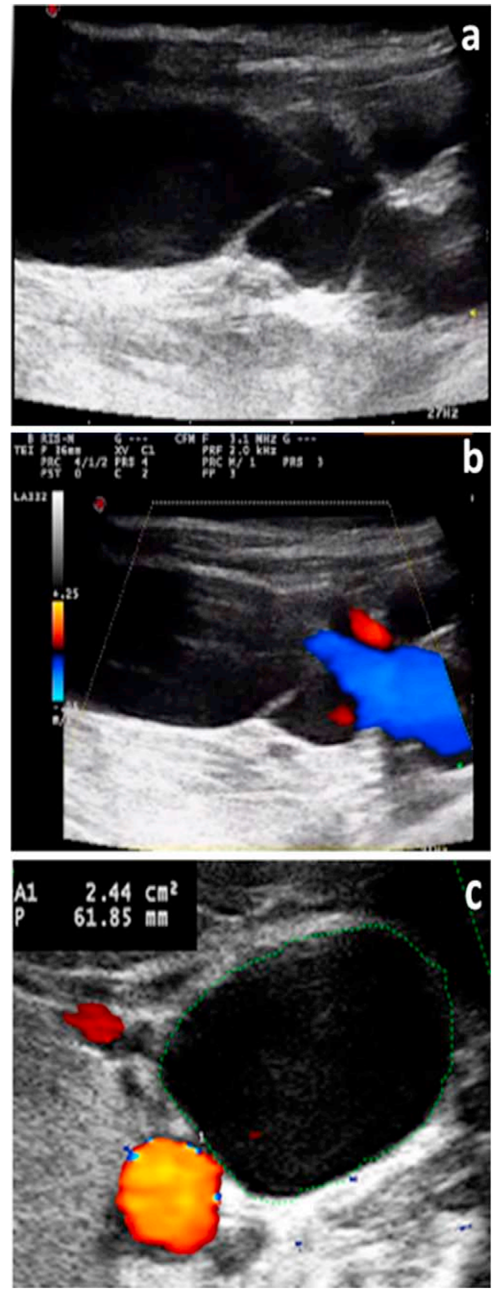

Figure 3 Example of an IJV stenosis at the valve level. (a) B-mode ultrasound examination of the IJV valve in their maximal opening position in longitudinal scan. (b) Color-mode ultrasound examination of the IJV valve in their maximal opening position in longitudinal scan. (c) CSA measurement at J2 IJV level in transverse scan.

the cerebral drainage pattern in single subjects, because of the wide variability of the contribution of jugular, vertebral routes of both sides and extrajugular—extravertebral routes.

For this protocol the blood flow is calculated in both supine and standing position for IJV and VV for the outflow and for ICA and VA for the inflow (only in the supine position), by applying the formula BF = CSA $\times$ TAV [4,16,17].

Criterion 5

The definition of this criterion is that CSA of IJV in upright position is larger than the one in supine position, being the normal condition the opposite one. Some authors questioned about a mistake for this criterion [4,7] and anyway a difference between right and left IJV in supine and upright position has been described in patients with transient global amnesia, because of the compression of the left brachiocephalic vein in the thoracic outlet [11].

This criterion has been proposed by Zamboni et al. [1,2] as a marker of the loss of venous compliance. In this protocol, considering the doubts expressed from other authors [4,7] also the deviation from the normal response to breath,

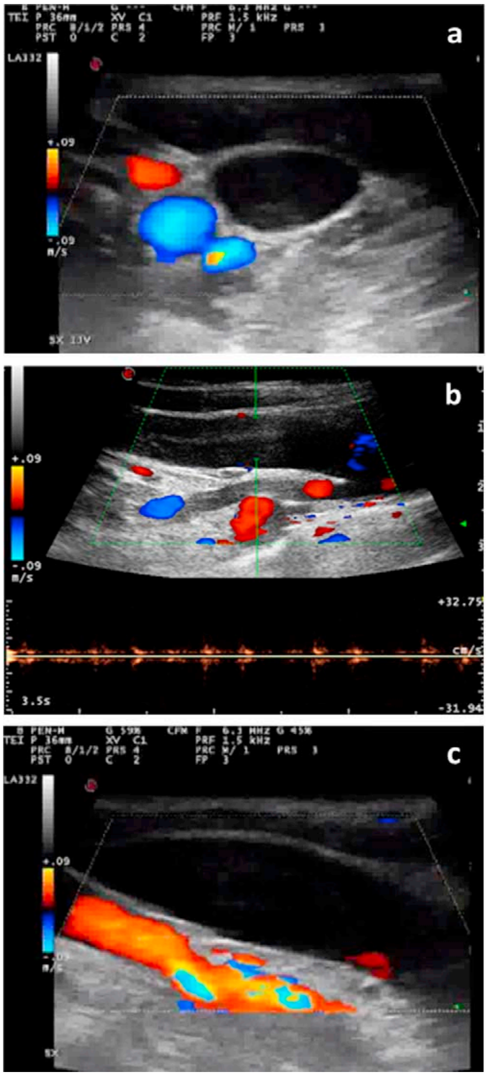

Figure 4 Example of the positivity of criterion 4. (a) Color-mode of the J2 IJV in transverse scan, showing the absence of color signal into the IJV lumen. (b) Corresponding Doppler waveform. (c) Color-mode of the J2 IJV in longitudinal scan, showing the absence of color signal into the IJV lumen.

with an increasing CSA during the inspirium phase and a decreasing CSA during the expirium phase, will be signaled, in order to better understand the global hemodynamic response.

Conclusions

The aim of the ultrasound study of the cerebral venous hemodynamics should be to understand the global hemodynamic responses and abnormalities, rather than to consider the alteration of the single segment of the single vein. For this aspect, it is possible that any criterion or combination of criteria cannot show this global view, but the blood flow study of inflow and outflow can help, in our opinion, to define a reliable and proper description of the global hemodynamics.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.permed.2012.03.013.

References

[1] Zamboni P, Galeotti R, Menegatti E, et al. Chronic cerebrospinal venous insufficiency in patients with multiple sclerosis. Journal of Neurology, Neurosurgery and Psychiatry 2009;80:392—9.

[2] Zamboni P, Menegatti E, Galeotti R. The value of cerebral Doppler venous haemodynamics in the assessment of multiple sclerosis. Journal of the Neurological Sciences 2009;282:21—7.

[3] Simka M, Kostecki J, Zaniewski M, Majewski E, Hartel M. Extracranial Doppler sonographic criteria of chronic cerebrospinal venous insufficiency in the patients with multiple sclerosis. International Angiology 2010;29:109—14.

[4] Doepp F, Paul F, Valdueza JM, Schmierer K, Schreiber SJ. No cerebrocervical venous congestion in patients with multiple sclerosis. Annals of Neurology 2010;68:173—83.

[5] Sundström P, Wåhlin A, Ambarki K, Birgander R, Eklund A, Malm J. Venous and cerebrospinal fluid flow in multiple sclerosis: a case-control study. Annals of Neurology 2010;68:255—9.

[6] Baracchini C, Perini P, Calabrese M, et al. No evidence of chronic cerebrospinal venous insufficiency at multiple sclerosis onset. Annals of Neurology 2011;69:90—9.

[7] Mayer CA, Pfeilschifter W, Lorenz MW, Nedelmann M, Bechmann I, Steinmetz H, Ziemann U. The perfect crime? CCSVI not leaving a trace in MS. Journal of Neurology, Neurosurgery and Psychiatry 2011;82:436—40.

[8] Nedelmann M, Eicke BM, Dieterich M. Functional and morphological criteria of internal jugular valve insufficiency as assessed by ultrasound. Journal of Neuroimaging 2005;15:70—5.

[9] Nedelmann M, Teschner D, Dieterich M. Analysis of internal jugular vein insufficiency — a comparison of two ultrasound methods. Ultrasound in Medicine and Biology 2007;33:857—62.

[10] Gisolf J, van Lieshout JJ, van Heusden K, Pott F, Stok WJ, Karemaker JM. Human cerebral venous outflow pathway depends on posture and central venous pressure. Journal of Physiology 2004;560:317—27.

[11] Chung CP, Hsu HY, Chao AC, et al. Detection of intracranial venous reflux in patients of transient global amnesia. Neurology 2006;66:1873—7.

[12] Chung CP, Hsu HY, Chao AC, Sheng WY, Soong BW, Hu HH. Transient global amnesia: cerebral venous outflow impairment-insight from the abnormal flow patterns of the internal jugular vein. Ultrasound in Medicine and Biology 2007;33:1727—35.

[13] Chung CP, Hsu HY, Chao AC, Wong WJ, Sheng WY, Hu HH. Flow volume in the jugular vein and related hemodynamics in the branches of the jugular vein. Ultrasound in Medicine and Biology 2007;33:500—5.

[14] Lichtenstein D, Saïfi R, Augarde R. The internal jugular veins are asymmetric. Usefulness of ultrasound before catheterization. Intensive Care Medicine 2001;27:301—5.

[15] Zamboni P, Galeotti R, Menegatti E, et al. A prospective open-label study of endovascular treatment of chronic cerebrospinal venous insufficiency. Journal of Vascular Surgery 2009;50:1348—58.

[16] Doepp F, Schreiber SJ, von Münster T, et al. How does the blood leave the brain? A systematic ultrasound analysis of cerebral venous drainage patterns. Neuroradiology 2004;46:565—70.

[17] Schreiber SJ, Lurtzing F, Gotze R. Extrajugular pathways of human cerebral venous blood drainage assessed by duplex ultrasound. Journal of Applied Physiology 2003;94:1802—5.